did find sequences on p. 128 that lacked sequence identifiers. The noted text on p. 128 disclosed that the p35 multimer derived from full length PDGF D included C-terminal fragments derived from SEQ ID NO:2 that had N-terminal sequences as provided in FIG. 15. These N-terminal sequences in FIG. 15 were properly labeled by SEQ ID NO, which are now incorporated into the text. Therefore, this oversight is now corrected, and Applicants respectfully request that the objection be withdrawn.

35 U.S.C. § 112, second paragraph, Rejections Overcome

Claims 1-26 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for referring to "PDGF D", "p35", and "p85", but not providing a particular sequence identifier for each variant. Claims 2, 8, 15 and 22 have been cancelled. Applicants traverse this rejection as applied to the remaining claims.

Independent claims 1, 7, 13 and 22 have been amended to refer to defined C-terminal fragments of SEQ ID NO:2. All other claims depend from these claims and incorporate this material by reference. Applicants assert that this rejection is now moot and request that it be withdrawn.

35 U.S.C. § 112, first paragraph, Rejections Overcome

Claims 20-26 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and inadequate written description. Applicants traverse this rejection as applied to the claims as pending.

The Examiner states that no guidance or objective evidence is provided to indicate that levels of PDGF D could be used for staging any type of cancer or indicating disease progression. *See*, Office Action p. 4. Applicants disagree with this characterization, and note that specific examples of staging cancers are disclosed throughout the application.

Example 7 (pages 117-120) discloses differential expression of the 30664188 transcript in normal tissues and cancer cells. See, *e.g.*, Table 7, pages 118-120. For example, 30664188 is differentially expressed when comparing, *e.g.*, various normal vs. cancerous cells from tissues including at least, *e.g.*, pancreatic cells (rows 4-5), CNS cancer cells (rows 19-27), lung cells (rows 58-69), ovarian cells (rows 76-82) or prostate (rows 86-87). Example 37 discloses differential serum concentration of the 30664188 polypeptide in patients with, *e.g.*, renal, lung, tongue or prostate cancers. See, *e.g.*, Table 15, pages145-146. It would be routine for a worker

skilled in the art to obtain or to determine the stages of the cancers in the tissues (Table 7) or patients (Table 15) disclosed therein.

Further, Example 38 on page 147 describes a specific method of staging cancers with the present invention. The specification recites that "samples of blood are taken from *subjects diagnosed as being at various stages* in the progression of the disease" (*see,* lines 2-3, emphasis added). Thus, these patients are afflicted with cancers that have already been staged by a previously standardized medical diagnosis. The Example continues, stating "The concentration of a 30664188 antigen present in the blood samples is determined using a method that specifically determines the amount of the antigen that is present" (*see,* lines 4-5). Assays for detection of the polypeptide and polynucleotide are referenced above. The Example then states "Using a population of samples that provides statistically significant results *for each stage of progression or therapy, a range of concentrations of the antigen that may be considered characteristic of each stage* is designated" (*see,* lines 6-9, emphasis added). Thus, the specification presents guidance on developing reference concentrations for the claimed antigen present in various cancers, that reflect different stages of disease progression. The derivation of such reference standards are routine for one skilled in the art, especially in view of the disclosure provided. There is no experimentation necessary to obtain these results, simply the performance of such assays.

The staging of a cancer in a subject under study, according to the claimed methods, is further taught by the specification. At page 147, Example 38 continues, stating "a sample of blood is taken from the subject and the concentration of a 30664188 antigen present in the sample is determined" (lines 11-12). This is accomplished using the techniques described in the specification, and include detection means for the polypeptide and polynucleotide encoding the 30664188 antigen, as described above. The staging of the patient's cancer is accomplished by comparison of the value of the antigen level seen in the patient to the value of the antigen level seen in the reference standards. The specification states "The concentration so obtained is used to identify in which range of concentrations the value falls" (*see,* page 147, lines 12-13). This is not an experimental technique. It is a routine assay, readily performed by a skilled practitioner, that provides unequivocal guidance on how to stage cancers using the claimed methods.

Applicants respectfully submit that the specification teaches the staging of cancers of at least these listed tissues by detection of either the claimed polypeptide or the polynucleotide

encoding the same. Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

35 U.S.C. § 102(a),(e) Rejections are overcome.

Claims 1-19 were rejected by the Examiner under 35 U.S.C. § 102(e) as being anticipated by the following PCT Publications: (a) WO 01/00878, whose international filing date is June 29, 2000; (b) WO 00/66736, whose international filing date is May 3, 2000; and (c) WO 00/27879, whose international filing date is November 10, 1999. Applicants traverse all three rejections.

Applicants submit that the §102(e) rejection has been applied incorrectly. According to the Office of Patent Legal Administration Pre-OG Notices: "Examination Guidelines for 35 U.S.C. § 102(e), as amended by the American Inventors Protection Act of 1999, and further amended by the Intellectual Property and High Technology Technical Amendments Act of 2002, and 35 U.S.C. § 102(g)" at URL: http://www.uspto.gov/web/offices/pac/dapp/opla/preognotice/ogtext102e.htm:

> ... A US or WIPO publication of an international application filed prior to November 29, 2000 will have no prior art effect under § 102(e). Such publications do, however, have prior art effect under § 102(a) or (b) as of their publication dates.

As all three references cited were filed prior to November 29, 1999, the references cannot be used to support a rejection under §102(e). However, if applied under §102(a), the rejection still cannot stand for the reasons presented below.

a) WO 01/00878, published January 4, 2001.

The Examiner states that WO 01/00878 anticipates the instant invention by teaching VEGF G, said to be identical to PDGF D, and antibodies to VEGF G. However, the instant application is a CIP application that claims priority to provisional patent application U.S.S.N. 60/158083, filed October 7, 1999, which discloses the PDGF D nucleotide and polypeptide sequences (FIG. 1), antibodies that bind immunospecifically to PDGF D, and uses thereof, namely:

> The invention is therefore useful in potential therapeutic applications, for a cDNA encoding the novel human growth factor may be useful in gene therapy, and novel human growth factor may be useful when administered to a subject in need thereof. The novel nucleic acid encoding the protein of the invention, or fragments thereof, may further be useful in diagnostic applications, wherein the presence or amount of the nucleic acid or the protein are to be assessed. These materials are further useful in the generation of antibodies that bind

immunospecifically to the novel substances of the invention in therapeutic or diagnostic methods.

See, U.S.S.N. 60/ 158083, page 2, final paragraph. Since WO 01/00878 was published later than the disclosure date for PDGF D, it is an improper citation under §102(a) and should be withdrawn.

Further, the WO 01/00878 reference does not anticipate the invention claimed. There is little teaching in the reference for how to treat and diagnose other than a conclusory statement, prophetic at best, that the molecules can act as a diagnostic target and therapeutic agent of cellular proliferative disorders such as cancer. Nor does this reference teach detection of the p35 antigen of the invention utilizing an antibody specific for the p35 protein.

The instant specification teaches actual and real application for treatment of cancers, for example, tongue cancer (see Specification p. 146). The significant effect of blocking expression of PDGF D antigen in cancer is further exemplified in Figure 24. Figure 24 shows the effect of neutralizing antibodies that bind to PDGFD and thereby block its expression compared to control antibodies.

In the specification on page 144, Example 36 clearly teaches detection of the p35 form of PDGF D (also referred to as 30664188) using an antibody that binds this molecule. This invention provides a highly specific and very sensitive assay for a PDGFD antigen by detection of increasing concentrations of antigen in a sample. *See*, *e.g.*, Table 14 on page 145 of the specification. The invention also discloses expression of the PDGF D antigen in specific cancers, which was not taught in the cited reference. *See*, *e.g.*, Table 15 on page 146 of the specification. Unlike the cited reference, Applicants have possession of the invention.

For the reasons described above, WO 01/00878 does not anticipate all elements of the invention claimed. Applicants respectfully request that it be withdrawn.

b) WO 00/66736, published November 9, 2000.

The Examiner states that WO 00/66736 anticipates the instant invention by teaching ZVEGF4, said to be identical to PDGF D, and the use of antibodies to ZVEGF4 for detection and quantification. However, as stated above, the instant application is a CIP application that claims priority to provisional patent application U.S.S.N. 60/158083, filed October 7, 1999, which discloses the PDGF D nucleotide and polypeptide sequences (FIG. 1), antibodies that bind immunospecifically to PDGF D, and uses thereof in therapeutic or diagnostic methods. *See*, *Id*,

reproduced above. Since WO 00/66736 was published later than the disclosure date for PDGF D, it is an improper citation under §102(a) and should be withdrawn.

Further, WO 00/66736 also fails to anticipate the invention claimed. The Examiner's reliance on page 57, lines 28-31 for showing diagnosis of cancer falls short of teaching the method of the invention. The statement regarding diagnosis of cancer in this reference is again, nothing more than a suggestion. Nor do the examples teach detection of the p35 antigen using an antibody that binds to p35.

This reference does not anticipate all elements of the claimed invention, and Applicants respectfully request that it be withdrawn.

c) WO 00/27879, published May 18, 2000.

The Examiner states that WO 00/27879 anticipates the instant invention by teaching PDGF D, said to be identical to the instant PDGF D, and the use of antibodies to PDGF D for detection and quantification. However, as stated above, the instant application is a CIP application that claims priority to provisional patent application U.S.S.N. 60/158083, filed October 7, 1999, which discloses the PDGF D nucleotide and polypeptide sequences, antibodies that bind immunospecifically to PDGF D, and uses thereof in therapeutic or diagnostic methods. *See, Id*, reproduced above. Since WO 00/27879 was published later than the disclosure date for the instant PDGF D, it is an improper citation under §102(a) and should be withdrawn.

Further, WO 00/27879 also fails to teach all elements of the claimed invention. The Examiner's relies on page 19, p. 24 lines 16-34, and p. 20 lines 11-13 for detection and quantitation by antibodies. However, the reference teaches the use of a truncated molecule prepared from residues 334-370 that has characteristics that differ from the PDGF D proteins of the invention. For instance, the truncated residues of the reference do not bind to VDGF receptors nor cause tyrosine phosphorylation of the PDGF beta receptor, in contrast to the PDGF D protein taught by the invention. Further, no other experimental results are provided other than the progressive cloning of the gene. More significantly, prophetic examples (see page 40) are provided to show methods for mitogenicity on endothelial cells and fibroblasts among other prophetic examples. Such examples suggest the inventor of this reference/invention did not possess the invention claimed.

This reference does not anticipate all elements of the invention, and Applicants respectfully request that it be withdrawn.

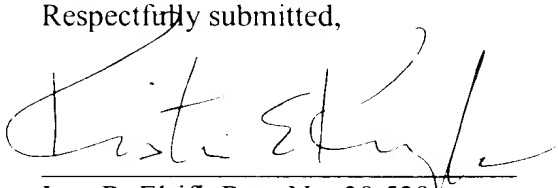
(d) WO 00/34474, published June 15, 2000

PCT publication WO 00/34474, whose international filing date is December 7, 1999, was made of record for teaching SEQ ID NO:37, said to be identical to PDGF D (SEQ ID NO:2). Because the WO 00/34474 application has an international filing date prior to November 29, 2000, and a publication date after October 7, 1999, the earliest priority date for PDGF D (SEQ ID NO:2), it cannot be cited as art under either §102(a) or (e).

CONCLUSION

The Commissioner is authorized to charge any additional fees that may be due, or to credit any overpayment, to the undersigned's account, Deposit Account No. 50-0311 Ref. No. 15966-577A CIP 3 (Cura-77A CIP 3). A duplicate copy of this transmittal letter is enclosed herewith.

Respectfully submitted,



Dated: November 27, 2002

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APPENDIX A: MARKED UP VERSION OF SPECIFICATION

Please amend the specification on page 128, lines 9-16, as follows:

-- Amino terminal sequence analysis of p35 demonstrated proteolytic cleavage after Arg247 (R247) or Arg249 (R249) residues of SEQ ID NO:2 (FIG. 15). As indicated in Panel A of FIG. 15, two peptides were found, one beginning with GlyArg (*i.e.* GRSYHDR ...(SEQ ID NO:23), shown with the [GR] Gly248-Arg249 residues underlined), which corresponds to the p35 polypeptide product resulting from a cleavage after R247 of SEQ ID NO:2, and the second beginning with the third residue, Ser250 (*i.e.* SYHDR ...), of SEQ ID NO:23, which corresponds to the p35 polypeptide product resulting from a cleavage after R249 of SEQ ID NO:2. The ratio of these peptides was found to be SYHDR:GRSYHDR = 4:1. The additional sequencing results in FIG. 15 (Panels B and C) (SEQ ID NOS:24-25, beginning with Gly248, and SEQ ID NOS:26-27, beginning with Arg341) indicate that further processing produces the remaining polypeptides seen with Coomassie blue staining but not with anti-V5 Westerns, namely the 16 kDa and 6 kDa species shown. These are joined together to provide p35. --

APPENDIX B: MARKED UP VERSION OF CLAIMS

Cancel claims 2, 8, 15 and 22 without prejudice and without disclaimer of the subject matter. Amend claims 1, 7, 13 and 20 as follows:

1. (Amended) A method of detecting the presence of at least one PDGFD antigen of SEQ ID NO:2 in a sample, comprising the steps of:

a) providing a biological sample;

b) contacting the sample with an agent that binds [the] to at least one p35 antigen, wherein the p35 antigen comprises at least one C-terminal fragment of SEQ ID NO:2, wherein the C-terminal fragment comprises an N-terminus beginning at Gly248, Ser250 or Arg341 of SEQ ID NO:2; and

c) detecting the presence of the agent bound to the p35 antigen;

whereby the presence of the agent indicates that the antigen is present in the sample.

7. (Amended) A method of determining the amount of at least one PDGFD antigen of SEQ ID NO:2 in a sample, comprising the steps of:

a) providing a biological sample,

b) contacting the sample with an agent that binds [the] to at least one p35 antigen, wherein the p35 antigen comprises at least one C-terminal fragment of SEQ ID NO:2, wherein the C-terminal fragment comprises an N-terminus beginning at Gly248, Ser250 or Arg341 of SEQ ID NO:2; and

c) determining the amount of the agent bound to the p35 antigen;

whereby the amount of the agent so determined correlates with the amount of the antigen in the sample.

13. (Amended) A method of contributing to a diagnosis of cancer in a subject, comprising the steps of:

i) providing a biological sample from the subject, and

ii) determining whether [at least one PDGFD antigen] at least one p35 antigen is present in the sample, wherein the p35 antigen comprises at least one C-terminal fragment of SEQ ID NO:2, wherein the C-terminal fragment comprises an N-terminus beginning at Gly248, Ser250 or Arg341 of SEQ ID NO:2;

whereby a finding that the antigen is present indicates that the subject may have cancer.

20. (Amended) A method of staging cancer in a subject, comprising the steps of:

a) providing a biological sample from the subject;

b) determining the amount of [at least one PDGFD] a p35 antigen in the sample, wherein the p35 antigen comprises at least one C-terminal fragment of SEQ ID NO:2, wherein the C-terminal fragment comprises an N-terminus beginning at Gly248, Ser250 or Arg341 of SEQ ID NO:2; and

c) correlating the amount with the stage of the cancer;

thereby staging the cancer in the subject.